REMARKS

The claims have been reproduced for the convenience of the Examiner. No amendments have been proposed.

Introduction.

Before arguing the outstanding rejections, applicants wish to remind the Office of their contribution to gene silencing technology. Applicants were the first to understand that, aside from what was known about double-stranded RNA in general as triggers of gene silencing, short RNA molecules in particular, are the effectors of gene silencing. As applicants state in their application on page 2:

> In every case a previously uncharacterized species of antisense RNA complementary to a targeted mRNA was detected. These RNA molecules were of a uniform length, estimated at around 25 nucleotides, and their accumulation required either transgene sense transcription or RNA virus replication. Corresponding sense RNA molecules were also detected.

And they state,

> There have been no previous reports of such short sense and antisense RNA molecules... that are detected exclusively in organisms exhibiting PTGS, possibly because (owing to their size) they could not have been readily detected by routine RNA analyses.

Applicants are quoting this because it appears that their contribution to the art has been lost sight of by the Office. As will be further argued below, neither Fire nor Graham nor Brown understood that it is short RNA molecules that mediate gene silencing. These workers may have recognized that short matching portions of longer RNA molecules might be involved in gene silencing, but there is no understanding that it is these short molecules that mediate this phenomenon. It is the specific contribution of

the applicants to have isolated these species from organisms that are exhibiting post-transcriptional gene silencing, and therefore understanding that these short molecules are the RNA molecules that are critical.

This has been recognized by the scientific community as well. Attached are reports of two awards conferred on Dr. Baulcombe, one of the inventors herein, for this very work. The Lasker Award is a prestigious U.S. award comparable to the Nobel Prize. A description of this award and of its selection of Dr. Baulcombe is attached as Exhibit A.

Dr. Baulcombe has also been awarded the 2008 Franklin Institute Medal in Life Science as shown in Exhibit B. The résumé on pages 3-5 of Exhibit B tells the story. Although a single-stranded 20-nucleotide RNA had been discovered in *C. elegans* in 1993 by Drs. Ambros and Ruvkun, this was not appreciated as contributing to gene silencing. Only after Dr. Baulcombe's (and Dr. Hamilton's) discovery of both sense and antisense short RNA's in plants undergoing post-transcriptional gene silencing was it understood that these short sense and antisense RNA's were instrumental in gene silencing.

Applicants request that these exhibits be considered. They could not have been earlier submitted since the awards were only recently conferred.

<u>The Rejection of Claims 125-130 Under 35 U.S.C. § 102(e) Over Graham (US 6,573,099)</u>.

Applicants understand that the teaching of Graham is not limited to its examples; however, these are not entirely irrelevant to what Graham teaches when taken as a whole. There is no dispute that the exemplified constructs of Graham that are relevant to the invention – *i.e.*, those that will generate sense and antisense RNA molecules, are much longer than 30 nucleotides. But the

Examiner is correct that the issue is whether Graham taken as a whole specifically teaches (not merely suggests) the production, from its constructs, of short RNA molecules 20-24 nucleotides in length as required by the present case. Graham does not teach this.

Graham Does Not Meet the Legal Standard for Anticipation of Claims 125-130.

In order to anticipate, each and every element of the claimed invention must not only be found in the cited document, the elements must be arranged and connected as described in the claim. This principle was recently followed in a District Court decision *Daiichi Pharmaceutical Co. v. Apotex*, 83 USPQ2d 1471 (DCNJ 2006) citing among other precedent, *ATD Corp. v. Lydall, Inc.*, 159 F3d 534, 48 USPQ2d 1321 (Fed. Cir. 1998) for the proposition that an anticipating reference must describe the patented subject matter sufficiently that its existence is recognized by persons of ordinary skill. The Daiichi court also cited *In re Arkley*, 455 F2d 586, 172 USPQ 524 (CCPA 1972) which overturned a rejection for anticipation of a claim to a single cephalosporin C_a compound over a disclosure of a genus which included it and also described specific examples of precursors which would lead to the compound of the claim if treated with a particular reagent which was also disclosed in the cited document. The Court overturned the anticipation rejection on the grounds that the reference did not clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without any need for picking, choosing and combining various disclosures not directly related to each other by the teaching of the reference.

Similarly, here, there is insufficient specificity in the teachings of Graham to lead the reader to understand that it would be desirable to produce short RNA molecules of 20-24 nucleotides, nor, indeed, that RNA molecules of that size would actually be produced by the DNA constructs described.

Every place in Graham that 20-30 nucleotides or even 30 nucleotides is mentioned, these are described as portions of DNA constructs of at least 30 nucleotides to be transcribed into RNA. Graham never describes constructs that contain DNA sequences that will be transcribed into molecules of only 20-24 nucleotides, nor does he describe short RNA molecules *per se* anywhere in his disclosure. Graham clearly teaches only constructs that will generate longer RNA, and clearly requires (see column 5, lines 7-20):

> [T]he only requirement being…the structural gene sequence of the synthetic gene is at least about 80%-90% identical to 30 or more contiguous nucleotides of the target gene

Thus, a minimum sequence of at least 30 nucleotides must be transcribed from the construct.*

This clearly contrasts with the unsupported statement on page 3 of the Office action, asserting: "However, clearly Graham does encompass structural gene components that when expressed produce RNA's that are at least 20-30 nucleotides in length." Applicants respectfully request that any location in Graham where it is shown that RNA's of even 30 nucleotides, let alone 20-30 nucleotides, are said to be produced, be identified.

There is not even any motivation in Graham to attempt to produce RNA of 20-24 nucleotides, since Graham states a minimum of 30 nucleotides is required in the DNA construct.

Graham states that the portion of the DNA to be transcribed contains a sequence that is at least 30 nucleotides long that is "substantially identical" to a "region" of a target gene. This is

* Whatever is intended by what is presented at column 6, lines 25-40 of Graham, which recites preferred structural gene components of the synthetic gene as comprising "at least about 20-30 nucleotides in length derived from " certain specified target genes must be read either to still meet the requirement of at least 30 contiguous nucleotides specified in column 5 and if not, introduces such ambiguity into what Graham is actually teaching as to inevitably make indefinite and ambiguous any statement about the length of any RNA's that might be produced when any of the Graham constructs are expressed.

precisely what Graham says in column 5, lines 7-20 – that it is a *requirement* that the synthetic gene is substantially identical at the nucleotide sequence level to at least part of the target gene (line 9). By "substantially identical" is meant that the structural gene sequence of the synthetic gene is at least 80%-90% identical to 30 or more contiguous nucleotides of the target gene more preferably, etc. (lines 12-20).

Thus, Graham is completely clear that the constructs themselves *must* include sequences to be transcribed that are at least 30 nucleotides long, clearly outside the scope of the requirement that the constructs of the present invention generate RNA molecules that are only 20-24 nucleotides long. As noted above, the examples use much longer sequences.

The Office focuses on sections of column 6 and of the claims which state that the structural gene *components* of the synthetic gene of the invention comprise at least about 20-30 nucleotides in length derived from a viral DNA polymerase, viral RNA polymerase, etc. These statements must be reconciled with the *requirement* set forth in column 5. These statements can be consistent only if one interprets them as referring to portions of the required 30-nucleotide sequences that are derived from the target gene. The "structural gene components" referred to in line 25 and in line 35-36 of column 6 must then refer to the required "substantially identical structural gene" of the synthetic gene which themselves are longer than 30 nucleotides, such that portions of them that are "derived from" the targeted gene are subsequences of these lengths. Thus, for example, if the structural gene portion is itself only 30 nucleotides in length, a portion of it – *e.g.*, a 20-nucleotide stretch might be derived from the referenced polymerases, but in addition, at least four additional nucleotides elsewhere in the 30 must be derived from the polymerase as well according to the *requirement* in column 5, for at least 80% identity. In other words, the 20-30 nucleotides does not refer to the

structural gene component itself *per se*, but rather to a portion thereof. The structural gene components which must be at least 30 nucleotides simply "comprise" the specified nucleotide lengths. The open language "comprise" allows the inclusion of additional nucleotide sequences that are also derived from the relevant gene. This will make the description in column 6 consistent with the *requirement* set forth in column 5.

This is also consistent with the claim language which requires substantial identity to at least a region of the target gene wherein the region is 20-30 nucleotides long. This can be reconciled with the requirement in column 5, if one assumes that the 20-nucleotide sequence simply refers to a reference point in the target gene, rather than the only sequence actually set forth in the construct.

Applicants hope that this intense parsing of the precise language of Graham does not obscure the main point – *that Graham never once refers to constructing vectors which will generate RNA molecules that are 20-24 nucleotides in length or to RNA molecules per se in this size class.*

Even if the Interpretation of the Office were Correct, Graham at Best Teaches a Large Genus of Constructs Where the Specified Lengths Refer to the Construct, Not the Generated RNA.

The Office takes the view that Graham does not teach that the structural gene component must be more than 20-30 nucleotides in length, but rather at least that long. However, as noted above, there is a *requirement* for at least 30 nucleotides. However, even if the Office were correct in its reading of Graham, this still falls short of anticipating the present claims. Even if applicants were to accept the interpretation of the Office that the transcribed portion of the gene constructs described in Graham could be as little as 20-24 nucleotides in length, Graham does not teach constructs which generate RNA molecules that must be within this size range. At best, Graham,

under this interpretation, teaches a genus containing a very large number of species, and the preferred embodiments are constructs that generate much longer RNA.

The disclosure of a genus with such large numbers of members does not anticipate or even render obvious a species unless that species is named. *In re Baird*, 16 F3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994). In this case, the species is not named as there is no explicit disclosure of producing RNA molecules of 20-24 (or 20-30) nucleotides. Graham never states explicitly that RNA molecules of 20-24 nucleotides will be generated by its constructs, therefore, this disclosure if present must be inherent. In order to establish inherency, the mere fact that a certain thing may result from a given set of circumstances is not sufficient (MPEP § 2112(IV) citing *In re Oelrich*, 666 F2d 578, 581-582, 212 USPQ 323, 326 (CCPA 1981)). It cannot be a matter of mere probabilities. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991).

In other words, to demonstrate that it is inherent that RNA molecules of 20-24 nucleotides would result from the constructs described in Graham, the Office must demonstrate that this is the inevitable result of these constructs. Obviously it is not, since the constructs are clearly required to contain DNA to be transcribed that is at least 30 nucleotides in length, and the transcribed DNA is permitted to be much longer.

Even if it is correct, as the Office further states, that Graham encompasses structural gene components that when expressed produce RNA's that are at least 20-30 nucleotides in length; this does not anticipate the present claims which require that the constructs generate RNA's that are precisely 20-24 nucleotides in length. At best, even according to the interpretation of the Office,

Graham discloses a wide range of sizes ranging from 20 nucleotides to much longer, at least as long as the BEV polymerase gene.

MPEP 2131.03 discusses anticipation of ranges. While the heading of section II of this passage says that prior art which teaches a range overlapping or touching the claimed range anticipates if the prior art range discloses the claimed range with sufficient specificity, the only case cited, *Atofina v. Great Lakes Chem. Corp.*, 441 F3d 991, 78 USPQ2d 1417 (Fed. Cir. 2006) is instructive. In this case anticipation was not found in a situation analogous to what the Office sees as the present case. In that case, the reference taught a temperature range of 100-500°C. The Court held that the claimed range of 350-450°C was not described with sufficient specificity to be anticipatory. That was true even where there was a slight overlap between the reference's preferred range (150-350°C) and the claimed range. As far as applicants can see, there is no preferred range disclosed in Graham (to the contrary, there is a stipulation in Graham of a requirement of at least 30 nucleotides which is, at best, relevant only to the uppermost range of as disclosed in the subject application) and the proximity of the limits of the ranges is much less than that in the cited case.

Summary.

Graham falls short of anticipating claims 125-130 because Graham never discloses either explicitly or inherently constructs that will produce short RNA molecules of 20-24 nucleotides total.

The Rejection of Claims 116-124 as Obvious Over Fire (US 6,506,559) in View of Graham.

In making this rejection, the Office states that claim 1 of Fire does not place any limit on the size of the double-stranded RNA molecule. This is exactly applicants' point. It is only applicants that have discovered that RNA molecules of this size are effective in causing gene silencing.

Even if the interpretation of the Office is correct, that Fire includes RNA molecules that are only 25 nucleotides in length as opposed to RNA molecules that simply have portions of 25 nucleotides in length that match targeted genes, Fire at best teaches a very large genus of RNA molecules that does not suggest focusing on molecules of 20-24 nucleotides. The Office correctly does not reject the present claims as anticipated by Fire, since Fire does not specifically suggest molecules of 20-24 nucleotides. Further, the Office does not assert that Fire alone suggests the invention, although asserting that the term "may be" at least 25, 50, etc., bases could encompass this range. (Of course, it is only the "length of the identical nucleotide sequences" that is referred to, not the RNA molecule itself.) Because of this language, and because of the remainder of the specification, Fire, when read as a whole, teaches away from RNA molecules even as short as 25 nucleotides.

While the teaching of Fire is not limited to its examples, clearly the exemplified RNA molecules would lead the reader to believe that much longer molecules are not only desirable, but required. Absolutely nothing is ever said in Fire about the length of RNA molecules that participate in gene silencing. In fact, there was a known problem, at the time of the Fire (and Graham) priority dates, with using long dsRNA in vertebrate or mammalian systems. Long dsRNA molecules were

known to induce an interferon response, resulting in the non-specific destruction of mRNA's.[†] Given this, if it were obvious at the time that SRMs (per the claimed invention) would have avoided this effect and would have been effective at inducing silencing, why did neither Graham nor Fire check to confirm the existence of such molecules (as was done by the present inventors), and why did they not explicitly disclose use of this size class of molecules (as is done in the present disclosure)? The only molecules that are exemplified are much longer. There is no discussion independent of the exemplified molecules of what the length of the molecules, as opposed to the matching portion of the molecules, should be.

Graham is apparently cited because applicants' claims are limited to short RNA molecules of 20-24 nucleotides which is shorter than the lower limit of the identical sequence (not molecules) set forth by Fire. The Office argues that Graham would permit extension to the range of 20-24 nucleotides because of the discussion in Graham of DNA constructs which include portions of identity with a targeted gene of 20-30 nucleotides. Graham, however, does not remedy the essential deficiency of Fire, which is that the length of the RNA molecules is not specifically taught, and Graham makes no suggestion to the contrary. As argued above, in reality, Graham specifically *requires* that the structural gene component of synthetic genes must be at least 30 nucleotides long

[†] The attached Exhibit C is merely to verify the state of the art as characterized here, if it is somehow doubted by the Office. The ability of long double-stranded RNA to induce interferon was summarized, for example, by Torrence, P. F., *et al., Pharmacol. Ther. Part A* (1977) 2:1-88 in particular on pages 3 (Table 1) and 18-24. The avoidance of the downstream problems associated with the presence of interferon by using short RNA is demonstrated by the work of Manche, L., *et al., Mol. & Cell Biol.* (1992) 12(11):5238-5248 already of record which demonstrates that activation of the protein kinase DAI is optimal when at least 85 base pairs are present resulting in the "virtually complete abrogation of protein synthesis" (see p. 5238, right-hand column, and p. 5240, right-hand column, under "Activation and Inhibition of DAI." This is further verified by Minks, M. A., *et al., J. Biol. Chem.* (1979) 254:10180-10183 which concludes that the enzymes 2′,5′oligo A polymerase and protein kinase could not be activated by dsRNA containing poly(C) shorter than 30 nucleotides and that maximal activation was obtained with dsRNA-containing poly(C) longer than 65-80 nucleotides. This paper also verifies the ability of double-stranded RNA to induce interferon referencing the enclosed Torrence paper and indicating that double-stranded RNA is a potent inhibitor of protein synthesis in interferon treated cells citing Kerr, I. M., *et al., Nature* (1974) 250:57-59.

in the construct, and, as was the case for Fire, nothing is taught in Graham about the size of RNA molecules that might be generated by the constructs set forth in Graham, except that Graham suggests that most constructs be polyadenylated and contain adenylation signals by virtue of the presence of a terminator, thus generating much longer RNA molecules.

Importantly, Graham, while implying that RNA will be transcribed intracellularly from the vectors, is completely silent on what requirements might be necessary should the RNA be supplied directly to the cells. Even if Graham is read to include (although certainly not to require) generation of RNA molecules intracellularly that are shorter than 25 nucleotides, Graham is devoid of suggestions as to what might be required should the RNA be supplied to the cells directly. There is no reason to believe that the size requirements would be the same in both cases.

In short, Fire teaches only methods for providing RNA directly to cells to silence genes, while Graham teaches only intracellular generation of RNA. The teachings of Graham and Fire are thus of limited relevance to each other and implications of the conditions surrounding the methods of one with respect to the other requires speculation.

The Rejection of All Claims as Assertedly Obvious Over Brown (US 6,723,897).

As an initial matter, Brown makes no suggestion whatsoever of administering RNA molecules directly to plants or cells or of administering vectors that will generate sense and antisense RNA. Brown merely mentions "cosuppression" without further description, so even if any length of nucleotide sequence were referenced to "cosuppression", it is speculative as to what is being associated with that length. In any event, Brown never postulates required nucleotide sequence lengths for cosuppression.

For this and other reasons set forth below, applicants cannot agree that "such as by" before "antisense expression" results in the implication that the sizes specified apply either to RNA molecules used directly in gene silencing or to RNA molecules generated by vectors used in gene silencing. On a factual level, if the minimum requirement is 12 contiguous nucleotides, this is dramatically smaller than what is said to be required by either Fire or Graham (or indeed the present application) as a minimal identical sequence. Second, Brown in the passage at issue at the bottom of column 3, lists antisense constructs, ribozymes, triplex DNA, cosuppression or "any other well known methods" for reducing expression. The paragraph goes on to state that particular enzymes might be silenced "such as by antisense expression of a sequence that comprises at least 12 contiguous nucleotides (and preferably more) of sequences enumerated which encode the various enzymes." Clearly, this length description cannot apply to all of the methods set forth earlier in the paragraph. Ribozymes and triplex DNA, for example, would not involve these sequences or their complements. The nexus between antisense and the number of nucleotides is quite explicit. To conclude that "the sizes apply to any molecules for cosuppression as well" simply contradicts what the paragraph says.

Every single time sequences of specified length are discussed in Brown, it is antisense RNA that is referred to. Column 5, lines 50-58, describe the length of antisense constructs as is made clear at line 60. This is entirely consistent with column 3 at lines 49-67, which was the section quoted in the previous response, that again refers the 12 contiguous nucleotides to an antisense technique. (Applicants assume that the Office meant lines 61-62, rather than columns 61-62). The presence of "such as" by antisense expression does not change the conclusion. The 12 contiguous

nucleotides clearly refers to antisense expression. There appears to be nothing at all in Brown that suggests any particular length of any molecules that might be used for "cosuppression."

Finally, and more importantly, the specific range of 20-24 nucleotides is clearly not suggested by Brown. Brown mentions a range of 12 nucleotides to full length encoding sequences. The considerations with respect to patentability of a small range within a much larger one as outlined above still apply. Most importantly, the Office appears to have overlooked the teaching of the present invention which requires that the RNA be between 20 and 24 nucleotides. This is a result of the discovery by applicants of RNA molecules of this size in plants which experience gene silencing. As shown by the present applicants, nucleotide sequences in this range are required. Molecules of only 12 nucleotides don't work. Thus, even if the Office interprets 12 nucleotides as referring to cosuppression (even assuming that Brown refers by cosuppression to sense and antisense RNA molecules), not only is this a misreading of the paragraph, it results in an unworkable result which is contradicted by the findings of the present applicants (and Fire and Graham).

For these reasons, Brown does not suggest the invention.

Conclusion.

It is the specific contribution of the present inventors that short RNA molecules of 20-24 nucleotides are critical in silencing genes. None of the cited documents either disclose or suggest this. Graham does not anticipate claims where the short RNA molecules are provided by intracellular expression because Graham fails to teach the use of vectors which specifically produce RNA molecules of 20-24 nucleotides, no more, no less. The combination of Fire and Graham does not render claims 116-124 obvious because, at a minimum, Fire is the only document that teaches

the use of RNA directly to silence genes and Fire, even if it disclosed the use of molecules of 25 nucleotides (which it does not), would not be subject to modification by the teaching of Graham since Graham does not teach anything about direct use of RNA molecules to silence genes. Brown does not suggest the claimed invention because those sections of Brown which refer to nucleotide sequence length clearly refer to the generation of antisense RNA by their own terms and the lower limits envisioned by Brown make no sense with respect to cosuppression because they are inoperable.

The point to keep in mind, once again, is that only the present inventors have demonstrated or realized that it is RNA molecules of uniform length of about 25 nucleotides that are responsible for gene silencing.

Therefore, applicants believe claims 116-130 are in a position for allowance and passage of these claims to issue is respectfully requested.

Should minor issues remain that could be resolved over the phone, a telephone call to the undersigned would be appreciated.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 616292000111.

Respectfully submitted,

Dated: September 29, 2008 By: / Kate H. Murashige /

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